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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/769,204	01/24/2001	Malcolm R. Alison	259/181US	4799

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LYON & LYON LLP
633 WEST FIFTH STREET
SUITE 4700
LOS ANGELES, CA 90071

EXAMINER
PAPPU, SITA S

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 08/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,204	ALISON ET AL.	
	Examiner	Art Unit	
	Sita Pappu	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26 and 27* is/are allowed.

6)☒ Claim(s) *28-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 26-51 are pending in the instant application. This Office Action is in response to the amendment filed by the Applicant on 06/24/2002 (Paper #8).

Response to the amendment

Claims 26, 28-32, 35, 40, 47, 49-51 are amended. Currently, claims 26-51 are under consideration.

The rejection of claims 28-51 under 35 U.S.C. 112, first paragraph, for lack of enablement has been withdrawn in light of Applicant's amendment and arguments.

The rejections of claims 26-51 under 35 U.S.C. 112, second paragraph have been withdrawn in light of amendments filed.

The requirement for a new Oath and/or Declaration is maintained.

Claims 28-51 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Response to arguments and New Grounds of rejection

In response to the requirement for a new Oath and/or Declaration, Applicant states that no new Oath is required because a copy of the oath or declaration from a prior non-provisional application may be filed even if the specification is different from that of the prior application. While this holds true for amendments made to the specification, when new claims are added by a preliminary amendment, as in the instant case, a supplemental oath is required. See MPEP 608.04(b).

Claims 28-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cirrhosis of the liver by improving the efficiency of in vivo liver cell retroviral transduction comprising inducing a semi-synchronous wave of in vivo liver cell proliferation by concurrently administering tri-iodothyronine (T3) and keratinocyte growth factor (KGF), and the method further comprising administering to the liver a retroviral vector complexed with cationic liposomes wherein the retroviral vector encodes hepatocyte growth factor or HGF, and wherein increased liver cell proliferation leads to amelioration of cirrhosis of liver, does not reasonably provide enablement for treating any disease associated with liver using any RNA, protein or polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In response to the rejection of claims 28-51 under 35 U.S.C. first paragraph, Applicant amended the claims and limited them to the treatment of diseases associated with liver (page 6, bottom paragraph) using any RNA, and protein or polypeptide and argues that the claims are enabled for treating cirrhosis (categories 2 and 3, pages 7 and 10) and that the claims thus satisfy the "how to use" requirement. Applicant further argues that gene therapy methods of the present invention are not unpredictably vague and that liver is an important organ for gene therapy (page 15). Applicant, in this context, makes references to Fujimoto (2000) and Ueki (1999) wherein a vector encoding HGF was shown to be effective in ameliorating cirrhosis of liver (page 17, bottom paragraph).

While the arguments are compelling in pointing out that administration of a vector encoding HGF is effective in treating or ameliorating cirrhosis of liver, and that the method of the instant invention would provide a method to increase the liver cell proliferation and thus contribute to the effectiveness of the treatment of cirrhosis of liver using a vector encoding HGF, the arguments are not found persuasive with respect to the use of the instant method of liver cell proliferation in treating any liver disease using any RNA or protein. Neither the Applicant's arguments nor the specification provide guidance on how any liver disease can be treated using the method of the invention. Further, there is insufficient guidance on treating any liver disease using any RNA or protein with the method of the instant invention.

Claims 28-51 are drawn to a method of treatment for any liver disease and to a method for treating or preventing cirrhosis of the liver by using the method of the invention. While the specification discloses a method for improving the liver cell transduction efficiency, by administering a composition comprising tri-iodothyronine (T3) and keratinocyte growth factor (KGF), which may be effective in treating cirrhosis of liver when used in conjunction with HGF, it does not disclose a method of treatment for any other liver disease. While the skill of an artisan in this subject area is considered very high, without specific guidance and/or working examples it would require undue experimentation on the part of a skilled artisan to practice the invention of claims 28-51 over the full scope.

While the method for improving transduction efficiency does increase the levels of transduction, the specification does not disclose how the increased transduction

levels would lead to the treatment and/or prevention of any disease of the liver in a subject. The specification does not teach how to use the invention as claimed. Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was not routinely successful and the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Further, as discussed in the previous Office Action, Davern et al. (1998; Digestive diseases, vol.16, pp23-37), in their review on "Gene Therapy for Liver Disease", highlight the obstacles that must be addressed before hepatic gene therapy becomes a reality (see abstract). Davern et al. (1998) state that efforts of gene therapy for correcting genetic defects in the liver and other organs have fallen short of the initially lofty expectations and that the gene therapy is a Herculean task when one considers that evolution has equipped all cells, normal or otherwise, to desperately resist such manipulation (page 35, concluding paragraph).

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acid vectors, and

the unpredictability of extending the results of animal systems to humans, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA in the cells, it would have required undue experimentation to practice the instant invention over the full scope and the skilled artisan would not have predicted success in treating or preventing diseases of the liver other than cirrhosis as claimed. Thus the specification does not enable one skilled in the art to use the claimed invention in a method for treating any liver disease.

Conclusion

Claims 26, 27 are allowable.

Claims 28-51 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application is assigned are (703) 308 4242 for regular communications. Any inquiry of a general nature or relating to the status of this application should be directed to the patent analyst, Tracey Johnson at (703) 305-2982.

S. Pappu
August 21, 2002

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER